REMARKS

The Examiner reopened prosecution in view of the appeal brief filed on March 24, 2003. Claims 3 and 5-13 are now pending in the present application. Applicants submit that claim 11 has been amended to more particularly point out and distinctly claim the subject matter which the inventors regard as the invention. The amendment is fully supported by the specification and claims as originally filed.

I. REJECTIONS UNDER 35 U.S.C. §101/112 FOR LACK OF UTILITY

The Examiner rejected claims 3 and 5-13 under 35 U.S.C. § 101 for a lack of patentable utility due to its not being supported by either specific and/or substantial utility or a well established utility.

The Examiner contends on page 3 of the Office Action that a "use" for physical and genetic mapping, or as a probe are utilities generic to the broad class of polynucleotides, and are therefore not specific, substantial and credible utilities for the particular polynucleotides claimed. The Examiner alleges that the specification does not disclose anywhere that any of SEQ ID NOS:9-18 are known to localize to a particular gene or chromosome, are known to be differentially expressed in particular tissues, or are known to be developmentally expressed and/or to regulate any stage of development. Applicants submit that lacking assertion of utility does not mean the invention has no utility. According to MPEP 2107, if the applicant has not asserted any specific and substantial utility for the claimed invention, rejections under 35 U.S.C.§ 101 and 112 shift the burden of coming forward with evidence to the applicant to: (i) explicitly identify a specific and substantial utility for the claimed invention; and (ii) provide evidence that one of ordinary skill in the art would have recognized that the identified specific and substantial utility was well-established at the time of filing. Specific and substantial utility for the claimed invention and evidence that one of ordinary skill in the art would have recognized that the identified specific and substantial utility was well-established at the time of filing are discussed below.

Applicants submit that according to the Guidelines for the Utility Requirement ("Utility Guidelines"), 66 FR 1098 Jan. 5, 2001; MPEP 2107.01, a claim to a polynucloetide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. According to the Utility Guidelines, a "specific utility" is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. The Utility

Guidelines indicate that since any gene can be used as a "gene probe" or "chromosome marker", there is a lack of specific utility if there is no specific DNA target. Accordingly, any gene or fragment of DNA sequence that is present in the human genome would fall within this broad class of the invention. However, as discussed in the Amendment filed on October 23, 2002 and January 17, 2002, Applicants submit that the gene trap method enriches for a class of genes that are not required for teratocarcinoma cell viability and are likely to be involved in late stages of cellular differentiation and development. As such, the claimed polynucleotides of the present invention can be used as a gene probe or chromosome marker *specific* for such genes that are of particular interest to scientists and medical practitioners studying the biology of cellular differentiation and development. As clearly set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

In fact, Applicants submit that the claimed polynucleotides are specifically identified and functionally validated exons (*i.e.*, exons which had been actually spliced during post-transcriptional processing) that would not have been identified by conventional molecular biology approaches. Exhibit A shows some exemplary sequence alignments of the claimed sequences with human genomic sequences in GenBank. As set forth in the specification, *inter alia*, at page 12, lines 11-27, the present invention provides tools for identifying exon splice junction, chromosome mapping, etc. This is one of the utility of the present invention as set forth throughout the specification as originally filed. The specification, *inter alia*, at page 20, lines 11-19, describes that the claimed polynucleotides from the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (e.g., splice acceptor and/or donor sites) that can be used in diagnostics. For example, as shown in Exhibit A, Applicants submit that SEQ ID NO:10 defines a coding region since SEQ ID NO:10 spans three distinct exons on chromosome 6 (bases 79194 to 78976; bases 82893 to 82772, and bases 82642 to 82549 from Genbank accession number AL035467 which is a clone from chromosome 6 separated by introns (bases 79193 to 82548, and bases 82643 to 82771 from Genbank accession number AL035467).

Applicants point out that only a small percentage (2-4%) of the human genome actually encodes exon sequences, and these exons are widely interspersed within a given chromosome. When the gene comprising these exons are expressed, the cell must remove the

introns from these exons and assemble them end-to-end in order to produce a functional mRNA which acts as a template for the translation of a protein product. The claimed polynucleotides comprising the sequence of SEQ ID NOS:9-18 encode exons that are actually spliced together to produce an active functional transcript. Thus, one of the utilities of the claimed sequences is for defining intron/exon splice-junctions. Exon splice junctions are particularly important in the study of disease and cancer because splice junctions are often hot spots for mutations and erroneous events leading to a disease state. Applicants respectfully submit that the practical scientific value of biologically validated, and spliced, mRNA sequences is readily apparent to those skilled in the relevant biological art.

In disclosing a functionally validated exon splice junction, the claimed polynucleotides provide physical evidence that effectively trumps the hypothetical and at times erroneous conclusions provided by bioinformatics analysis of the corresponding genomic region conducted without supporting physical data. As discussed above, the claimed polynucleotides define the intron/exon splice-junctions of genes which produce functional transcripts. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

The Examiner further alleges that the specification does not disclose that any of the SEQ ID NOS:9-18 are known to localize to a particular gene or chromosome. Applicants submit that each of the sequences of the present invention can be used to map a specific region on a specific human chromosome. The specificity of each of the claimed polynucleotides are listed below: SEQ ID NO:9 can be used to map a specific exon of human chromosome 5, due to the fact that SEQ ID NO:9 aligns with a clone from chromosome 5 (Genbank accession numbers AC020728.4.1.201404); SEQ ID NO:10 can be used to map three exons of human chromosome 6, due to the fact that SEQ ID NO:10 aligns with a clone from chromosome 6 (Genbank accession number AL035467); SEQ ID NO:11 can be used to map a specific exon of human chromosome 7, due to the fact that SEQ ID NO:11 aligns with two clones from chromosome 7 (Genbank accession numbers AC099759.4.101955 and AC005061.2.1.114828); SEQ ID NO:12 can be used to map a specific exon of human chromosome 20, due to the fact that SEQ ID NO:12 aligns with a clone from chromosome 20 (Genbank accession number AL034548.25.1.153170); SEQ ID NO:13 can be used to map a specific exon of human chromosome 11, due to the fact that SEQ ID NO:13 aligns with two clones from chromosome 11 (Genbank accession numbers AP002006.5.167355 and AP001981.5.1.183476); SEQ ID NO:14 can be used to map a specific exon of human chromosome 5, due to the fact that SEQ ID NO:14 aligns with a clone from chromosome 5 (Genbank accession numbers AC008536.7.1.178056); SEQ ID NO:15 can be used to map a specific exon of human chromosome 12 and chromosome 14, due to the fact that SEQ ID NO:15 aligns with a clone from chromosome 12 (Genbank accession number AC073576) and

a clone from chromosome 14 (Genback accession number AL355916); SEQ ID NO:17 can be used to map a specific exon of human chromosome 8, due to the fact that SEQ ID NO:17 aligns with a clone from chromosome 8 (Genbank accession number AC091022.4.1.155949); SEQ ID NO:18 can be used to map a specific exon of the human chromosome 13, due to the fact that SEQ ID NO:18 aligns with three clones from human chromosome 13 (Genbank accession number AF440620; AL158195, and AC005949).

The presently claimed polynucleotides have specific utility in mapping the protein-encoding regions of the corresponding segment of human chromosome, as described in the specification, *inter alia*, at page 12, lines 11-27. The exquisite specificity of each of the claimed polynucleotides for their specific locus on a corresponding human chromosome is evidenced by the fact that each of the claimed polynucleotides do not align properly and specifically with any other human genomic sequences. Hence, the claimed polynucleotides are not random fragments of genomic DNA of unknown location. Thus, the present sequences clearly meet the utility requirements of 35 U.S.C. § 101.

While earlier mapping techniques have identified gross chromosomal positions for numerous disease-associated genes, these techniques are inadequate to precisely map these genes. However, using the presently described nucleotide sequence and a computer system, the exact location of such disease-associated genes can be specifically pinpointed, as detailed above. The claimed polynucleotides provide exquisite specificity in localizing a specific region of a particular human chromosome that contains a validated exon, a utility not shared by virtually any other random pieces of nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. The skilled artisan readily appreciates the significant benefit afforded by markers, such as the present polynucleotides, that provide information on coding regions at a specific locus of the human genome. As such, the claimed polynucleotides have specific utility.

The Examiner alleges that Applicants argued on page 7 of the appeal brief filed March 24, 2003 that "every gene in the genome, when disrupted, necessarily provide the specific utility . . . ." The Examiner alleges that this appears to be an admission that any gene in the genome, when disrupted, would have the same utility as that argued for SEQ ID NOS:9-18. Contrary to the Examiner's allegations. Applicants submit that page 7, line 23 of the appeal brief in fact states "not every gene in the genome, when disrupted, necessarily provide the specific utility . . ." (emphasis added).

The Examiner contends that applicants fail to specifically identify the "specific class" of genes to which the claimed polynucleotides belong. While the asserted utility is not as narrowly defined as that of a correlation with a disease condition, and although the number of

polynucleotides that have such a specific utility is relatively larger than that of polynucleotides associated with a Mendelian genetic disease, Applicants submit that, it is nevertheless *not* a general utility that would be applicable to the broad class of genes in the genome. As such, Applicants submits that the claimed invention meets the threshold requirement of having specific utility.

The Examiner contends that mere knowledge or disclosure of what a gene does not do is not a disclosure for what the gene does do, or what activities it may regulate. Applicants submit that when a gene does not do a certain thing that is done in many genes, it takes the gene out of the broad class of genes in the genome. Accordingly, the gene no longer belongs to a broad class of genes in the genome and belongs to a subset of genes within the broad class of genes. The genes do *not* have a general utility, but a specific utility.

Since the Applicants have asserted specific and substantial utility for the claimed invention, *inter alia*, on page 10, line 32 to page 11, line 11 of the specification, the Examiner is required to establish a *prima facie* case for lack of specific and substantial utility. The Guidelines for the Utility Requirement provides that where the asserted utility is not specific or substantial, a *prima facie* showing must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The *prima facie* showing must contain the following elements (see MPEP 2107(II)(C)(1) and 2107.02(IV)) : (1) an explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial nor well-established; (2) support for factual findings relied upon in reaching this conclusion; and (3) an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. The Examiner has not provided any factual findings in which the conclusion for lack of specific and substantial utility is relied upon, nor has the Examiner evaluated utilities taught in the closest prior art. Accordingly, the Examiner has not provided a *prima facie* showing that the invention does not have specific and substantial utility. The rejection is thus in error and should be withdrawn.

The Examiner contends that the instant specification does not disclose that SEQ ID NOS:9-18 are known to be involved in regulation of differentiation or development of any cell type, nor has applicant provided any evidence to support this argument. However, Applicants submit that according to MPEP 2107.02(VII), evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. The character and amount of evidence needed to support an asserted utility will vary depending on whether the asserted utility appears to contravene established scientific principles and beliefs. *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967); *In re*

Chilowsky, 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956). Applicants have provided support derived through scientific logic to show that the gene trap method enriches a class of genes that is involved in late stages of stem cell differentiation and development as discussed in the remarks filed October 23, 2002.

The Examiner further contends that Applicants' argued that the polynucleotides can be used in cell-based systems to identify compounds which may be involved in development and cell differentiation disorders, but does not specifically identify sequences which are associated with said disorders, nor does the specification disclose that any sequences have been identified which have been used in such a cell-based assay. According to applicable case law, applicants do not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980). The Examiner is apparently questioning the credibility of the statement and not the credibility of utility. However, it is unclear what is the Examiner's basis for disbelieving Applicants' assertion. Applicants submit that, at least in regard to the requirements to show pharmacological activities for a compound, a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices. *Fujikawa v. Wattanasin*, 93 F.3d 1559; 39 USPQ2d 1897 (Fed. Cir. 1996). In fact, all that is required in evaluating the credibility of an asserted utility is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). A preponderance of the evidence exists when it suggests that it is more likely than not that the assertion in question is true. *Herman v. Huddleston*, 459 U.S.375, 390 (1983). Still further, according to the Guideline, office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Accordingly, the assertion that the genes identified in the present invention may be involved in the late stages of stem cell differentiation and development absent any countervailing evidence, satisfies the threshold of the utility requirement.

The Examiner contends on page 4 of the Office Action that a "use" for doing further research is not considered a specific, substantial, and credible utility. In the present application, the utility of the claimed invention would be immediately appreciated by those familiar with the technological field of the invention such as biologists studying cellular differentiation and development. Applicants submit that, among other uses, the polynucleotides of the present invention may be used as a research tool in the context of a hybridization assay,

e.g., in the format of a microarray. Instead of using the entire universe of genes in the genome in such an experiment, the skilled person has the option of limiting the experiment to using polynucleotides of the invention in the microarray. In effect, genes that are critically essential to the survival and early growth of teratocarcinoma cells would be excluded from the microarray. The use of polynucleotides of the present invention help cut down the total number of genes that needs to be studied and simplify the work of a biologist who uses this research tool to study embryonic cell differentiation and development. Thus, no further research is required to identify or reasonably confirm the asserted utility. Applicants submit that the guidelines cautioned not to interpret "immediate benefit to the public" to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. *Brenner v. Manson*, 383 U.S., 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility. Here, the set of genes that are enriched for their lack of involvement in cell viability and their likelihood of participating in the late stages of embryonic cell differentiation and their development represents substantial utility to biologists who are studying late stages of cellular differentiation and development. The preselected set of genes are currently available and will immediately provide, at a minimum, the economic benefit of not having to put every gene in the genome on microarray(s). Accordingly, the present invention has substantial utility.

For the claimed utility to be credible, the invention must be "believable based on the record or the nature of the invention" M.P.E.P. 2107.02(III)(A). Applicants assert that because of the nature of the invention and for the reasons set forth above, the utility of the claimed polynucleotides are specific, substantial and credible. Applicants respectfully request that rejection under 35 U.S.C. § 101 be withdrawn.

Claims 3, and 5-13 are also rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking utility. Applicants submit that when an Applicant satisfactorily rebuts a rejection based on a lack of utility under 35 U.S.C. § 101, the corresponding rejection imposed under 35 U.S.C. §112, first paragraph, should also be withdrawn. Thus, Applicants respectfully request that the rejection of claims 3, and 5-13 under 35 U.S.C.§ 112, first paragraph, be withdrawn.

II. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH FOR LACK OF ENABLEMENT

Claims 3 and 5-13 are rejected under 35 U.S.C.§112, first paragraph, as failing to comply with the enablement requirement. The Examiner alleges that the instant specification does not actually disclose how to use any of SEQ ID NO:9-18 in particular. As discussed above, Applicants submit that the specification teaches using the presently claimed polynucleotides in mapping the protein encoding regions of the corresponding human chromosome, as described in the specification, *inter alia*, at page 12, lines 11-15. The Examiner alleges that it would require undue experimentation by one skilled in the art to determine how to use the claimed polynucleotides to detect a polymorphism or to diagnose or detect a disease or disorder. Applicants submit that it is not necessary that the claimed polynucleotides have to detect a polymorphism or to diagnose or detect a disease or disorder. As indicated in MPEP 2164.01(c), when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. If any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention. Since the specification teaches at least one enabling use, enablement requirement is satisfied. Applicants respectfully request that the rejection of claims 3, and 5-13 under 35 U.S.C.§112, first paragraph, be withdrawn.

III. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH FOR LACK OF WRITTEN DESCRIPTION

Claims 3 and 10-13 are rejected under 35 U.S.C.§112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner alleges that the claimed polynucleotides may comprise repetitive sequences, and, potentially, entire genes or coding regions not disclosed by the instant specification. The Examiner further alleges that the fact that one skilled in the art can identify and distinguish polynucleotides based on hybridization properties does not constitute a written description of the polynucleotides, sequence, structure, etc. so identified. This is contrary to the requirement under case law that "the Applicant must convey with reasonable clarity to skilled persons, that inventor possessed invention, as later claimed." *Vas-Cath Inc. v. Mahurka* 1935 F.2d 1555, 19USPQ2d 1111 (Fed. Cir. 1991). "Although [the applicant] does not have to describe exactly the subject matter claimed, . . . the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-Cath* at 1116. Furthermore, case law also supports the fact that for chemical material, when one skilled in the art can distinguish a formula from others and can identify many of the species that the claims encompass, there is adequate description of the claimed genus. *Hybritech v. Monoclonal Antibodies*, 802 F.2d 1367, 1384, 231 USPQ 81, 94;

Fonar Corp. v. General Electric Co., 107 F.3d 1543, 1549, 41 USPQ2d 1801, 1805. In the present case, Claim 3 recites nucleotides that comprise a contiguous stretch of at least about 60 nucleotides of at least one of SEQ ID NOS: 9, 12-14, and 16-18. As the exact structure of SEQ ID NOS: 9, 12-14, and 16-18 are provided in the specification, although there are numerous polynucleotides that falls within this description, a person of skill in the art can readily recognizes the polynucleotide as described in claim 3. Likewise, Claim 13 describes a genus of polynucleotides by a property (*i.e.*, hybridizable under defined conditions to known sequences) that readily distinguishes the claimed polynucleotides from other materials. One of skill in the art can readily compare a polynucleotide with the claimed polynucleotides of Claim 13 by performing a hybridization as recited in the claim. As such, Applicants submit that adequate written description has been provided for Claims 3 and 10-13.

Claims 10-11 and 13 are rejected under 35 U.S.C.§112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges that the terms "at least about 30 nucleotides", "at least about 40 nucleotides", and "at least about 40 nucleotides capable of hybridizing . . ." are new matter. The Examiner alleges that the originally filed specification teaches on page 4 that oligonucleotides may comprise "at least about" 50, 75, 100, or 130 nucleotides and that on page 16, the sequences may comprise contiguous stretches of "at least" 30, 40, or 60 nucleotides. Further, the Examiner alleges that page 16 does not teach a contiguous stretch of "at least about" any length of nucleotides. Applicants submit that page 16 of the specification does indeed recite "at least 8, or at least 10, or at least 14, or at least 20, or at least 30, or at least about 40, and preferably at least about 60 consecutive nucleotides up to about several hundred bases of nucleotide sequence or an entire GTS sequence" (emphasis added). Applicants submit that in order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *in haec verba* support for the claimed subject matter at issue. See *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570, 39 USPQ2d 1895, 1904 (Fed. Cir. 1996). Applicants submit that no new matter was added to claims 10-11, and 13. Applicants respectfully request that rejection of these claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. REJECTION UNDER 35 U.S.C.§ 102(b) AS ANTICIPATED BY HILLIER

Claim 11 is rejected under 35 U.S.C.§ 102(b) as being anticipated by Hillier (NCBI accession number R91187). The Examiner alleges that Hillier teaches a polynucleotide sequence comprising a contiguous stretch of 35 nucleotides which are identical to residues 6-40 of instant SEQ ID NO:12. In response, Claim 11 has been amended to delete SEQ ID NO:12. Accordingly, the amended claim is not anticipated by Hillier. Applicants respectfully request that rejection of this claim under 35 U.S.C.§ 102(b) be withdrawn.

CONCLUSION

Applicants submit that Claims 3 and 5-13 satisfy all of the criteria for patentability and are in condition for allowance. Accordingly, Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application.

Respectfully submitted,

Date: December 16, 2003

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Enclosures